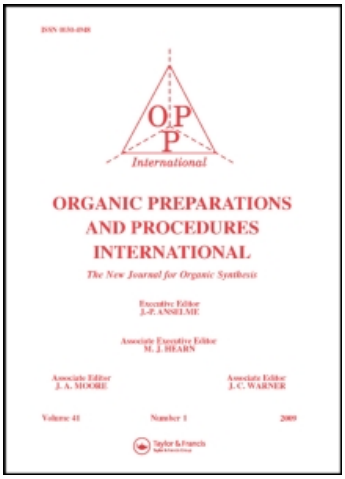

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A Convenient Method for the Synthesis of 3,5,6-Trisubstituted-2-chloropyridines with *bis*-(Trichloromethyl) Carbonate

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A Convenient Method for the Synthesis of 3,5,6-Trisubstituted-2-chloropyridines with *bis*-(Trichloromethyl) Carbonate

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The pyridine ring system is found in a large number of naturally occurring alkaloids and synthetic products of biological interest.[1–4] Therefore, continuing studies forward the synthesis of pyridines are important in the field of drug design. As shown in *Figure 1* , 3,5,6-trisubstituted-2-chloropyridines have been extensively used as versatile building blocks for the synthesis of many heterocyclic systems with potential biological activity.[5,6]

The Vilsmeier-Haack reaction has evolved into a powerful synthetic tool for the construction of many important heterocyclic compounds such as quinolines,[7] indoles,[8] quinazolines,[9] pyridines,[10] etc. Typically the reactions of active methylene compounds with Vilsmeier type reagents afford β-chloromethyleneiminium salts or β-chlorovinyl aldehydes,[11] which have been recognized as useful intermediates in heterocyclic synthesis. Recently, Asokan and co-workers have reported a method for preparation of 2-chloronicotinonitriles in three-component reactions under Vilsmeier conditions.[12] However, this approach still has room for improvement because of the use of phosphorus trichloride, the long reaction time, and the unsatisfactory yields.

As a white stable solid, *bis*-(trichloromethyl) carbonate (BTC) has emerged as a versatile readily handled and safer alternative for the synthesis of some important organic compounds.[13] In light of our recent success using this reagent,[14–22] herein, we provide an improved method for the preparation of 3,5,6-trisubstituted-2-chloropyridines from simple enolizable ketones and aliphatic nitriles using BTC and DMF for the generation of the Vilsmeier reagent *(Scheme 1).*

Exploratory experiments determined that the best ratio of acetophenone (**1a**) to BTC/DMF in 1,2-dichloroethane should be 1:1:3. In comparison with the reported methods

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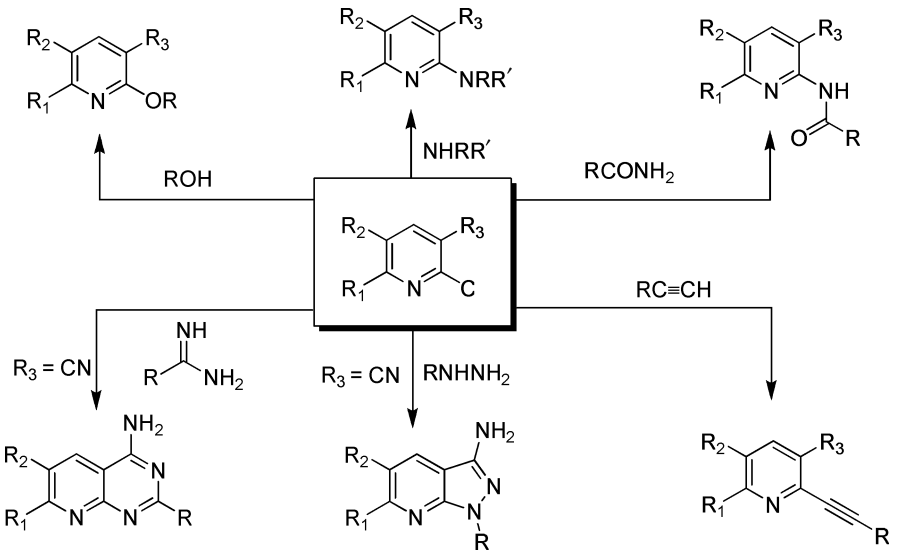
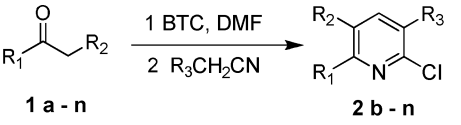


Figure 1
Various applications of 3,5,6-Trisubstituted-2-chloropyridines



a) $R_1 = C_6H_5$, R_2 = H, R_3 = CN; b) $R_1 = p$-$CH_3C_6H_4$, R_2 = H, R_3 = CN; c) $R_1 = p$-$CH_3OC_6H_4$, R_2 = H, R_3 = CN; d) $R_1 = p$-ClC_6H_4, R_2 = H, R_3 = CN; e) $R_1 = m$-ClC_6H_4, R_2 = H, R_3 = CN; f) $R_1 = p$-FC_6H_4, R_2 = H, R_3 = CN; g) $R_1 = p$-$NO_2C_6H_4$, R_2 = H, R_3 = CN; h) $R_1 = m$-$NO_2C_6H_4$, R_2 = H, R_3 = CN; i) $R_1 = C_6H_5$, $R_2 = CH_3$, R_3 = CN; j) R_1 = styryl, R_2 = H, R_3 = CN; k) R_1 = 4-chlorostyryl, R_2 = H, R_3 = CN; l) $R_1 = C_6H_5$, R_2 = H, R_3 = COOEt; m) $R_1 = m$-ClC_6H_4, $R_2 = CH_3$, R_3 = CN; n) $R_1 = p$-$CH_3C_6H_4$, R_2 = H, R_3 = COOEt;

Scheme 1

using phosphorus oxychloride,[12] our procedure has some advantages such as higher yields and more environmentally friendly. A variety of 3,5,6-trisubstituted-2-chloropyridines were obtained in relatively good yields *(Table 1)*. Enolizable ketones bearing electron-withdrawing groups (*e. g.* p-$NO_2C_6H_4$) or electron-donating groups (*e. g.* p-$CH_3OC_6H_4$) proceeded in relatively lower yields. While enolizable ketones with neutral substituent groups (*e. g.* p-$CH_3C_6H_4$, p-ClC_6H_4) proceeded in good to excellent yields. The structures were confirmed by ^{1}H-NMR, IR, MS and elemental analysis[23] and those of compounds **2m** and **2n** were further confirmed by ^{13}C NMR and MS *(Table 2)*.

In summary, an improved method for preparation of 3,5,6-trisubstituted-2-chloropyridines using BTC and DMF as Vilsmeier reagent has been developed.

Experimental Section

Melting points were obtained on a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. ^{1}H

Table 1
Synthesis of 3,5,6-Trisubstituted-2-chloropyridines using BTC and DMF

Product[a]	Yield (%)	mp (°C) (*lit*. m.p.)	IR (cm^{-1})	^1H NMR (δ)
2a	72	110–112 (112–114[12])	3040 2220 1580	7.31 (d, 1 H, $J = 11.2$ Hz, PyH), 7.47–7.55 (m, 3 H, ArH), 7.80 (d, 2 H, $J = 8.4$ Hz, ArH), 8.08 (d, 1 H, $J =$ 11.6 Hz, PyH)
2b	79	122–124	3113 2222 1617	2.44 (s, 3 H, CH_3), 7.27–7.31 (m, 3 H, PyH, ArH), 7.70 (d, 2 H, $J = 8.0$ Hz, ArH), 8.07 (d, 1 H, $J = 11.2$ Hz, PyH)
2c	56	140–142	3129 2210 1642	3.90 (s, 3 H, OCH_3), 6.98–7.01 (m, 2 H, ArH), 7.40 (d, 1 H, $J = 8.8$ Hz, PyH), 7.47 (d, 1 H, $J = 12.4$ Hz, ArH), 7.79 (d, 1 H, $J = 8.8$ Hz, ArH), 8.06 (d, 1 H, J = 11.6 Hz, PyH)
2d	68	140–141	3122 2228 1620	7.30 (s, 1 H, PyH), 7.43 (t, 1 H, $J = 8.0$ Hz, ArH), 7.51 (d, 1 H, $J = 8.4$ Hz, ArH), 7.67 (d, 1 H, $J = 8.0$ Hz, ArH), 7.77 (m, 1 H, ArH), 8.05 (d, 1 H, $J = 11.2$ Hz, PyH)
2e	62	132–134	3126 2231 1617	7.30 (s, 1 H, PyH), 7.43 (t, 1 H, $J = 8.0$ Hz, ArH), 7.52 (d, 1 H, $J = 8.4$ Hz, ArH), 7.67 (d, 1 H, $J = 8.0$ Hz, ArH), 7.77 (s, 1 H, ArH), 8.05 (d, 1 H, $J = 11.2$ Hz, PyH)
2f	71	95–97	3127 2230 1574	7.18 (t, 1 H, $J = 8.8$ Hz, PyH), 7.24 (d, 2H, $J = 12.4$ Hz, ArH), 7.80–7.84 (m, 2 H, ArH), 8.05 (d, 1 H, J = 11.6 Hz, PyH)
2g	56	122–124	3118 2224 1610	7.23 (d, 1 H, $J = 12.0$ Hz, PyH), 7.32 (d, 1 H, $J = 12.0$ Hz, ArH), 7.63 (d, 2 H, $J =$ 8.8 Hz, ArH), 8.33 (s, 1 H, PyH), 8.38 (d, 1 H, $J = 9.2$ Hz, ArH)

(Continued on next page)

Table 1
Synthesis of 3,5,6-Trisubstituted-2-chloropyridines using BTC and DMF *(Continued)*

Product[a]	Yield (%)	mp (°C) (*lit*. m.p.)	IR (cm^{-1})	^1H NMR (δ)
2h	50	125–127	3121 2222 1613	7.36 (d, 1 H, $J = 11.2$ Hz, PyH), 7.72 (d, 1 H, $J = 7.6$ Hz, ArH), 8.06–8.11 (m, 2 H, ArH), 8.41 (d, 1 H, $J = 8.4$ Hz, PyH), 8.64 (s, 1 H, ArH)
2i[b]	58	100–102	3131 2224 1617	2.52 (s, 3 H, CH_3), 7.31–7.36 (m, 3 H, ArH), 7.38–7.52 (m, 3 H, PyH, ArH)
2j	60	244–246	3133 2226 1617	6.93 (d, 1 H, $J = 11.6$ Hz, CH = CH), 7.00 (d, 1 H, $J = 15.2$ Hz, CH = CH), 7.40 (m, 3 H, PyH, ArH), 7.47–7.52 (m, 3 H, ArH), 8.01 (d, 1 H, $J = 11.6$ Hz, PyH)
2k	63	240–242	3132 2230 1616	6.93 (d, 1 H, $J = 11.6$ Hz, CH = CH), 7.00 (d, 1 H, $J = 15.2$ Hz, CH = CH), 7.40 (m, 3 H, PyH, ArH), 7.47–7.52 (m, 2 H, ArH), 8.01 (d, 1 H, $J = 11.6$ Hz, PyH)
2l	73	124–126	3129 1715 1598	1.39 (t, 3 H, $J = 6.8$ Hz, CH_3), 4.34–4.40 (m, 2 H, CH_2), 7.32 (d, 1 H, $J = 12.0$ Hz, PyH), 7.46–7.50 (m, 3 H, ArH), 7.78–7.81 (m, 2 H, ArH), 8.44 (d, 1 H, $J = 11.6$ Hz, PyH)
2m[b]	65	110–112	3128 2231 1618	2.52 (s, 3 H, CH_3), 7.16 (d, 1 H, $J = 7.6$ Hz, ArH), 7.30–7.43 (m, 3 H, ArH), 7.49 (d, 1 H, $J = 8.0$ Hz, PyH)
2n	80	142–144	3131 1724 1617	1.38 (t, 3 H, $J = 7.2$ Hz, CH_3), 2.42 (s, 3 H, CH_3), 4.34–4.39 (m, 2 H, CH_2), 7.25–7.31 (m, 4 H, PyH, ArH), 7.70 (d, 1 H, $J = 8.4$ Hz, ArH), 8.44 (d, 1 H, $J = 11.6$ Hz, PyH)

a) Yellow solids unless otherwise stated. b) White solid.

Table 2
Elemental Analysis for Compounds **2b**–**2n**[23]

Compound **2**	Elemental Analysis Calcd (Found)		
	C	H	N
2b	68.28(68.36)	3.97(3.92)	12.25(12.22)
2c	63.81(63.94)	3.71(3.68)	11.45(11.42)
2d	57.86(57.97)	2.43(2.41)	11.25(11.23)
2e	57.86(57.95)	2.43(2.42)	11.25(11.26)
2f	61.95(62.08)	2.60(2.58)	12.04(12.01)
2g	55.51(55.40)	2.33(2.34)	16.18(16.20)
2h	55.51(55.39)	2.33(2.30)	16.18(16.16)
2i	68.28(68.11)	3.97(3.98)	12.25(12.21)
2j	69.86(70.05)	3.77(3.74)	11.64(11.62)
2k	61.12(61.25)	2.93(2.94)	10.18(10.16)
2l	64.25(64.39)	4.62(4.62)	5.35(5.34)
2m[a]	59.34(59.18)	3.06(3.05)	10.65 (10.67)
2n[b]	65.44(65.28)	5.12(5.11)	5.08 (5.09)

a) MS(EI): m/z(%) 262 (M^+, 15), 264 ($[M + 2]^+$, 6), 266 ($[M + 4]^+$, 2),192 (100); ^{13}C NMR($CDCl_3$): δ 17.3, 112.4, 114.1, 128.2, 129.0, 129.7, 130.4, 130.7, 131.3, 135.3, 138.1, 149.6, 156.6. b) MS(EI): m/z(%) 275 (M^+, 6), 277 ($[M + 2]^+$, 2), 212 (100); ^{13}C NMR($CDCl_3$): δ 14.1, 21.3, 61.5, 113.1, 119.3, 123.9, 127.4, 129.0, 129.7, 135.7, 139.7, 150.2, 155.2, 160.0, 162.0.

NMR spectra were measured on a Varian Mercur plus-400 spectrometer (400 MHz) in $CDCl_3$ using TMS as internal standard. ^{13}C NMR spectra were determined in $CDCl_3$ on Varian Mercur plus-100 spectrometer (100 MHz) with TMS as internal standard. Mass spectra were obtained on a Trace DSQ mass spectrometer *(Table 1)*. Elemental analysis was performed on a VarioEL-3 instrument. All chemicals were obtained from commercial sources *(Table 2)*.

General Procedure for the Preparation of 3,5,6-Trisubstituted-2-chloropyridines

The Vilsmeier type reagent was prepared by the slow addition of a solution of BTC (0.3 g, 1 mmol) in $ClCH_2CH_2Cl$ (4 mL) to DMF (0.3 mL, 3 mmol) in $ClCH_2CH_2Cl$ (4 mL) at 0°C followed by stirring at room temperature for 20 min. Then appropriate enolizable ketone **1** (1 mmol) was added. The resulting mixture was heated to 60°C and maintained at that temperature for 6 h, followed by addition of the nitrile (2 mmol) and heating reflux for 2 h. After completion of the reaction, the mixture was poured into saturated $NaHCO_3$ (50 mL), and extracted with ethyl acetate (30 mL × 3). After evaporation of the organic solvent, the residue was subjected to column chromatography on silica gel. Elutions with petroleum ether/ethyl acetate = 20:1 afforded the pure products.

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